REMARKS

This response is provided in response to the Office Action mailed on June 4, 2004, and the references cited therewith. Applicant notes that in response to the restriction requirement dated March 11, 2004, claims 7-22 are withdrawn without prejudice. Claims 1-6 are now pending in this application.

Claim 1 has been amended to clarify the subject matter of the invention. Support for the subject matter of claim 1 can be found throughout the specification, for example, in Figure 1 and at pages 22-27 and in the Examples.

Information Disclosure Statement

The Examiner has noted that listings of references in the specification are not proper information disclosure statements. Applicant has submitted an Information Disclosure Statement (with 1449 form) on December 20, 2001 and Supplemental Information Disclosure Statements and 1449 Forms on April 28, 2003, January 20, 2004 and May 28, 2004. While the Examiner has kindly initialized and returned copies of several of these 1449 forms, Applicant's Representatives have received copies of only pages 4 and 6 of the April 28, 2003 1449 form. Applicant respectfully requests that initialed copies of the April 28, 2003 and May 28, 2004 1449 forms be returned to Applicants' Representatives to indicate that the cited references have been considered by the Examiner.

§112, Second Paragraph, Rejection of the Claims

Claims 1-6 were rejected under 35 USC § 112, second paragraph, as allegedly indefinite because claim 5 does not have method steps. Claim 5 is directed to the labeled proteinoid microsphere of claim 1 that is synthesized for signal amplification or diagnostic imaging. Applicant submits that claim 5 is a product claim rather than a method claim as the Examiner has alleged. In particular, claim 5 further defines certain structural features relative to claim 1. For example, a labeled proteinoid microsphere that is synthesized for signal amplification would likely have the signal on the outside of the microsphere, whereas a labeled proteinoid microsphere that is synthesized for diagnostic imaging may have the label on the inside of the

microsphere. Other structural differences would likely exist for labeled proteinoid microspheres that are synthesized for signal amplification or diagnostic imaging.

Applicant submits that the language of claims 1-6 is definite and requests withdrawal of this rejection under 35 USC § 112, second paragraph, of claims 1-6.

§103 Rejections of the Claims

Claims 1-6 were rejected under 35 USC § 103(a) as allegedly unpatentable over Milstein et al. (U.S. Patent No. 6,413,550) in combination with Lee et al. (U.S. Patent No. 6,191,278).

Claims 1, 2, 5 and 6 were rejected under 35 USC § 103(a) as allegedly unpatentable over Fiege et al. (U.S. Patent No. 6,660,843) in combination with Khoobehi et al. (U.S. Patent No. 5,437,274).

Claims 3-4 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Milstein et al. (U.S. Patent No. 6,413,550) and Lee et al. (U.S. Patent No. 6,191,278) in view of Mathiowitz et al. (U.S. Patent 5,271,961).

The above rejections under 35 USC § 103(a), with respect to the references cited, are respectfully traversed.

Claim 1 is directed to a labeled proteinoid microsphere comprising a mixture of amino acids that are condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, a metal, or an enzyme, wherein the label is linked to the proteinoid microsphere.

Claim 3 is directed to the labeled proteinoid microsphere of claim 1 wherein the proteinoid microsphere is formed by thermal condensation of a mixture of amino acids in the presence of a crosslinking agent.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings to as to arrive at the claimed invention. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations (M.P.E.P. § 2143). The teaching or suggestion to arrive at the claimed invention and the reasonable expectation of success must both be found in the prior art, not in Applicant's

disclosure (M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Applicant submits that a *prima facie* case of obviousness cannot be established from the combination of cited references because the references do not teach all the claim limitations, there is no reasonable expectation of success that the references could produce the claimed invention and there is no suggestion or motivation to combine the references so as to arrive at the claimed invention.

Milstein et al./Lee et al. Rejection

According to the Examiner, Milstein et al. disclose proteinoid microspheres that are prepared by thermal condensation of amino acids. The Examiner cites to the Milstein et al. disclosure at col.2, lines 5-12 and col. 6, lines 32-40 as proof of these contentions. However, the Examiner admits that Milstein et al. fail to teach proteinoid microspheres that have a label comprising a fluorophore and contends that Lee et al. disclose rhodamine dye reagents (fluorophores) that can be used to label microspheres or can be incorporated into microspheres during their formation, citing to Lee et al. at col. 4, lines 39-61.

Applicant submits that neither Milstein et al. nor Lee et al. disclose a labeled proteinoid microsphere comprising a mixture of amino acids that are condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, a metal, or an enzyme. Milstein et al. are limited to disclosure of proteinoid carriers that encapsulate biologically active agents (e.g. pharmaceuticals). Milstein et al. provide no disclosure or teaching on microspheres with a label. Moreover, Milstein et al. is limited to encapsulation of the biologically active agent, so that it can be released at selected sites, for example, at selected sites in the gastrointestinal tract. See, e.g., Milstein et al. at col. 2, lines 42-49; col. 5, lines 29-39. Milstein et al. provide no disclosure or teaching that the biologically active agent (much less a label) should be linked to the proteinoid microsphere. Such linkage would defeat the purpose of the proteinoid carriers provided by Milstein et al., which is to deliver pharmaceutical agents to particular portions of the gastrointestinal tract. *See, e.g.*, Milstein et al., col. 2, lines 42-46.

Lee et al. are limited to disclosure of certain water-soluble rhodamine dyes and provide no disclosure or teaching that such dyes should be used with proteinoid microspheres made from a condensed mixture of amino acids.

Applicant submits that one of skill in the art would not be motivated to combine the teachings of Milstein et al. relating to releasable encapsulated biologically active agents with those of Lee et al. on rhodamine dyes, to produce the present invention relating to labeled proteinoid microspheres, wherein a label is linked to the proteinoid microsphere. Nor is there any teaching or suggestion to combine these references within Milstein et al. or Lee et al. to thereby arrive at the claimed invention, as is required by law. *See,* M.P.E.P. § 2143, citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 1-6.

Fiege et al./Khoobehi et al. Rejection

According to the Examiner, Fiege et al. discloses proteinoid microspheres that can contain a derivatized reagent that contains a spectral label. The Examiner cites Fiege et al. at col. 45, lines 10-37, as evidence of such a disclosure or teaching. The Examiner admits that Fiege et al. fail to teach labels such as fluorophores, chemiluminescent molecules, radioisotopes, paramagnetic ions, metal or enzymes. However, according to the Examiner, Khoobehi disclose particles that comprise such a dye. The Examiner cites Khoobehi at col. 9, lines 53-68, as evidence thereof.

Applicant submits that Fiege et al. provide no teaching on proteinoid microspheres whatsoever. Nor do Fiege et al. disclose any labels whatsoever. Fiege et al. are limited to a disclosure of fusions of a biologically active peptide and an Fc domain that are used solely as therapeutic agents. The text cited by the Examiner provides no disclosure or teaching on proteinoid microspheres or labels. Instead, col. 45, lines 10-37 is directed to derivatized amino acid residues to "improve the solubility, absorption, biological half life, and the like of the compounds." See Fiege et al., col. 44, 13-19. Fiege et al. also teach that the derivatizing moieties "may alternatively eliminate or attenuate any undesirable side-effect of the compounds

and the like." *Id.* Applicant submits that such disclosure is not a disclosure of proteinoid microspheres or of labels that may be linked thereto.

Moreover, even if Fiege et al. mention the two words "proteinoid microsphere" at some undisclosed location within the eighty-eight columns of text provided by Fiege et al. reference, such brief mention does not constitute a "teaching" that would guide one of skill in the art to the present invention, particularly in view of the remaining eighty-eight columns of text that are directed solely to modified peptides as therapeutic agents. The thrust of Fiege et al. is clearly directed towards therapy, not detection or labeling of target molecules. The thrust of Fiege et al. is clearly directed to specific peptide entities that can modulate the activity of a protein of interest. *See* Fiege et al., Tables 2-20 (providing numerous listings of many pharmacologically active peptides). Applicant submits that one of skill in the art would succumb to exhaustion before finding reference to proteinoid microspheres in Fiege et al. and loose all motivation to combine Fiege et al. with any other reference relating to labeling proteinoid microspheres or detection of target molecules with such labeled proteinoid microspheres. A two word disclosure of "proteinoid microsphere" surely cannot guide one of skill in the art to the present invention.

Similarly, Khoobehi et al. provide no disclosure of proteinoid microspheres. Instead, Khoobehi et al. is directed to methods of visualizing submicron size vesicles in blood. Khoobehi et al. define such submicron size vesicles as liposomes. See, Khoobehi et al., col. 4, lines 57-59. Khoobehi et al. also mention that particles such as cell walls or microcapsules can be used. See Khoobehi et al., col. 4, lines 59-62. However, Khoobehi et al. provide no recognition, disclosure or teaching on proteinoid microspheres whatsoever.

Nor is there any teaching or suggestion within Fiege et al. or Khoobehi et al. to combine these references and thereby arrive at the claimed invention, as is required by law. *See,* M.P.E.P. § 2143, citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Applicant submits that Fiege et al. in combination with Khoobehi et al. does not produce the claimed invention and respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 1, 2, 5 and 6.

Milstein et al./Lee et al./Mathiowitz et al. Rejection

As described above, Milstein et al. are limited to disclosure of proteinoid carriers that encapsulate biologically active agents (e.g. pharmaceuticals) and that can deliver such biologically active agents to selected sites within the gastrointestinal tract. Milstein et al. provide no disclosure or teaching on microspheres with a label.

As also described above, Lee et al. are limited to disclosure of certain water-soluble rhodamine dyes and provide no disclosure or teaching that such dyes should be used with proteinoid microspheres made from a condensed mixture of amino acids.

Mathiowitz (U.S. Patent No. 5,271,961) is limited to disclosure of methods for making protein microspheres by mixing a solution of proteins (not amino acids) while evaporating the solvent. As indicated by the Examiner, Mathiowitz discloses that the proteins employed can be cross-linked with cross-linking agents, however, the cross-linking agents are used to cross-link proteins, not the condensed amino acids of the present proteinoid microspheres. Hence, Mathiowitz does not disclose or teach proteinoid microspheres made of amino acids. One advantage to the use of amino acids is that amino acids do not give rise to an immune response, whereas proteins and peptides can give rise to problematic immune responses and other adverse side effects.

Applicant submits that one of skill in the art would not be motivated to combine the teachings of Milstein et al. on biologically active agent encapsulated in proteinoid microspheres for delivery to selected sites in the intestine with the teachings of Lee et al. on certain rhodamine dyes and the teachings of Mathiowitz on microspheres made from cross-linked proteins to somehow derive the present invention relating to labeled proteinoid microsphere comprising a mixture of amino acids that are condensed in the presence of a cross-linking agent, wherein the label is linked to the proteinoid microsphere. None of the Milstein et al., Lee et al. or Mathiowitz references provide any teaching or suggestion to combine these references and thereby arrive at the claimed invention, as is required by law to establish obviousness. *See,* M.P.E.P. § 2143, citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Therefore, Applicant submits that the combination of Milstein et al., Lee et al. or Mathiowitz references does not produce the claimed invention. Applicant requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 3 and 4.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

STEPHEN QUIRK

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Date October 4, 2004 By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 4 day of October, 2004.

Gina M. Uphus _____

Name

Signature